Canad. M. A. J.
Nov. 4, 1961, vol. 85

CLINICAL STAFF CONFERENCE

PHEOCHROMOCYTOMA

UNIVERSITY HOSPITAL,
SASKATOON, SASK.
MARCH 23, 1961

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DR. I. M. HILLIARD.* It has been possible to assemble today people from various departments who contributed to the diagnosis or treatment of pheochromocytoma in the patient to be presented. This multidepartmental approach reflects the many facets of this intriguing tumour first described by Fraenkel in 1886.

Considering that only 626 cases had been reported up to January 1957,[1] this tumour is certainly not common. However, it is not to be missed because it is one of the rare, really curable causes of secondary hypertension. These tumours are probably more frequent than the figure just quoted would suggest. I am sure some of us have seen cases which have not been reported, but it is unlikely that anyone has seen enough to have acquired a really valid personal experience with them. Even in large centres more than one dozen cases are seldom seen during many years. The largest series, 51 patients, was reported by Kvale *et al.* from the Mayo Clinic[2] and a series of 36 cases was reported in Scandinavia by von Euler and Ström.[3] The lack of solid personal experience with pheochromocytoma, coupled with its erratic clinical behaviour, results in diagnostic and therapeutic insecurity. This is another reason why we thought it would be interesting to present an apparently typical case which would show the difficulties and pitfalls awaiting the physician and surgeon.

CASE HISTORY

Mrs. O.D. (Hospital No. 66841), a 49-year-old married woman, entered hospital on February 24, 1961, for investigation of hypertension first discovered in August 1960.

Her family history was unremarkable, as was her past history until 1954, the year of her last delivery. Her three pregnancies were uncomplicated. Shortly after, she began to complain of paroxysmal periodic headaches and increasing shortness of breath on exertion, but did not consult her physician. There are no records of her blood pressure level between the time of her last pregnancy and August 1960. At that time, she was admitted to her local hospital because of the sudden onset of right anterior chest and right upper quadrant pain associated with chills, fever, nausea and vomiting. Blood pressure on admission was 260/130-140 mm. Hg. She improved on antibiotics within six days. Her ocular fundi remained normal, but her blood pressure was high (260/140) throughout her stay in hospital.

Investigations at that time showed albuminuria 4+, and 3-5 pus cells and 3-5 red blood cells per high-power field. The blood urea value, initially 60 mg. %, rose to 174 mg. % within three days of her admission and decreased, along with the albuminuria, within three weeks' time. An electrocardiogram (ECG) showed left ventricular strain pattern. A chest radiograph showed an irregular band area in the right base considered to represent pulmonary infarction. A retrograde pyelogram was normal.

After her discharge, her blood pressure was controlled with reserpine and hydrochlorothiazide and maintained at an average of 180/110 mm. Hg. She was re-examined in November 1960 and in January 1961. The sedimentation rate was consistently elevated up to 90 mm. in the first hour. Urine analysis continued to show a few red blood cells in the sediment, but no protein.

The paroxysmal headaches which began after her last pregnancy in 1954 were different in nature from any headaches she had ever had in the past. They were of sudden onset. The severe gripping pain began in the occipital area and neck, spread over the head, and was associated with intense heart pounding. The attacks lasted from thirty minutes to two hours and would sometimes occur just before her menstrual period. Some of the attacks were precipitated by hurrying, emotions, and sometimes by a hot bath, but frequently there was no obvious cause for them; some were followed by intense hunger and thirst. They varied in intensity. She had six or seven particularly severe attacks, one of which was observed in this hospital on March 7, 1961. It occurred suddenly between 8.00 and 9.00 a.m. and was accompanied by profuse sweating, nausea, weakness and anxiety. Her blood pressure was 260/140. She looked pale and shaky. An intravenous injection of 5 mg. phentolamine resulted in a prompt and persistent drop in blood pressure to 125/80.

Since her pneumonia in August 1960, she had tended to sweat profusely, sometimes continuously for several hours. This required at times a change of pyjamas twice a night. The sweating was not necessarily associated with headaches.

Between attacks, she felt relatively well apart from being tense, nervous and short of breath on exertion. Her appetite remained good. There was a loss in weight of approximately 10 lb. over five years. She had no visual complaints. She had no chest pain, nocturnal

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dyspnea or nocturia. She tended to be dizzy on getting up quickly from bed or on changing position. She tolerated heat poorly.

Physical examination disclosed a thin, tense woman weighing 98½ lb. Blood pressure on the first examination was 274/132-140 mm. Hg in both arms in the prone position. Pulse was 82 per minute and regular. She had no pyrexia. Fundi showed well-delineated discs with the central vein pulsating. There was an increase in light reflex of the arteries, marked segmental narrowing and moderate arteriovenous (A-V) nicking. A harsh grade three systolic precordial murmur was transmitted to the neck and axilla and was maximal in the left parasternal area. There was a diffuse left ventricular heave. The left heart border was located in the fifth intercostal space close to the anterior axillary line. The second aortic sound was markedly accentuated. Peripheral pulses were felt in all areas. On examination of the abdomen, there was slight guarding in the right epigastric area, and a mass, which could have been the kidney, was palpated in the right flank.

After admission, the patient was taken off all medication, for investigative purposes. Blood pressure in the prone position varied greatly, ranging from 270-170 systolic/130-110 diastolic. On standing, there was often a drop in blood pressure to as low as 140/95.

Results of Tests and Investigations

Hb. 12 g., P.C.V. 39%, R.B.C. 4,300,000, W.B.C. 4100 with a normal differential, and E.S.R. 91 mm. in the first hour. Serum proteins—total 6.7 g./100 ml. (albumin 3.4, total globulins 3.2; gamma globulin 1.3 g./100 ml.).

On urine analysis, the specific gravity in random specimens ranged from 1.015 to 1.020 and maximal specific gravity was 1.022. There was no proteinuria except during an attack of hypertension. In the urinary sediment occasional red cells and white blood cells were found. Urine culture was negative. B.U.N. was 21 mg./100 ml. Serum electrolytes were within normal limits.

B.M.R. was +21 and +29, and blood cholesterol 255 mg./100 ml. Protein-bound iodine was 5.5 μg. per 100 ml. Radioactive iodine uptake showed a low normal value of 12%.

Glucose tolerance curve was normal. Fasting blood levels ranged from 108 to 110 mg. per 100 ml.; the peak was at one hour at 165; the two-hour value was 112 and three-hour value 106 mg. per 100 ml. There was no glycosuria. During the attack of hypertension, blood sugar was 168-155 mg. per 100 ml.

TABLE I.—EXCRETION OF 3-METHOXY-4-HYDROXYMANDELIC ACID (VMA) AND R VALUES*

Mrs. O.D., Hospital No. 66841.

	R. values†		*VMA (μg./mg. creatinine)*	
	Mean	*Range*	*Mean*	*Range*
Normal subjects	2.09	1.58-2.26	1.6	0.7- 2.5
Essential hypertension	1.82	1.42-2.25	1.5	0.5- 4.0
Pheochromocytoma	0.74	0.45-1.16	16.0	7.5-30.0
Patient, Mrs. O.D.				
Preoperative, March 1961		0.71-0.92		
Postoperative, April 7/61		1.82		

*According to Gitlow *et al.*[1].

†The optical density of the final tested sample is determined spectrophotometrically at wave length 450 mμ and 550 mμ. The ratio (R) of Density 450 and 550 is related to the content of VMA in the sample as the Density 550 increases with VMA concentration. For details consult original paper.[1]

TABLE II.—CATECHOLAMINE EXCRETION (μg. per 24 hours)

Mrs. O.D., Hospital No. 66841.

Days before operation	*NA*	*A*	*Total*
13	232	130	362
12	271	199	470
11	298	203	501
10	714	145	859
Days after operation			
2	120	41	161
3	86	30	116
4	57	24	81

Phentolamine (Rogitine) tests were repeatedly consistent with pheochromocytoma. A histamine test was strongly positive. Base-line blood pressure was 180/115. Although only 0.0125 mg. of histamine base was injected intravenously (one-quarter of the recommended dose), there was a rise of systolic blood pressure within 30 seconds to at least 300 and 170 mm. Hg diastolic, and all manifestations of her spontaneous attacks were reproduced. Two injections of 5 mg. phentolamine were required to bring the attack under control. Urinary 3-methoxy-4-hydroxymandelic acid (Table I) and the 24-hr. output of catecholamines (Table II) were elevated.

ECG showed sinus rhythm, a rate of 70 per minute, left ventricular hypertrophy and strain.

Chest x-ray showed a moderate degree of left ventricular enlargement. Intravenous pyelography showed prompt excretion of the dye in good concentration. Retroperitoneal gas insufflation was suggestive of a nodule in the left adrenal area (Figs. 1 and 2).

Course in Hospital

On March 7, 1961, she had a major hypertensive attack as described. On March 11 and March 27, she had lesser attacks, during which her blood pressure was 280-270/150.

On March 15, the patient underwent an exploratory operation of the left retroperitoneal space; no tumour was found and the left adrenal, which was removed, was normal. She remained hypertensive.

On April 6, a laparotomy was performed and a chromaffin tumour located between the duodenum and the lower pole of the kidney was removed. The right adrenal gland was normal.

Postoperative Condition

Following the second operation, her blood pressure fell initially to 140 systolic/90 diastolic and stabilized at 155-160 systolic/90 diastolic in the prone position. On standing, it was 140 systolic/88 diastolic. She felt more relaxed and ceased to perspire. Physical examination 12 days after operation showed no changes in the funduscopic examination. The precordium appeared quieter, but cardiac findings were otherwise unchanged. On electrocardiogram, considerably lower voltages in the left precordial leads were noted and there was some regression of ST-T changes.

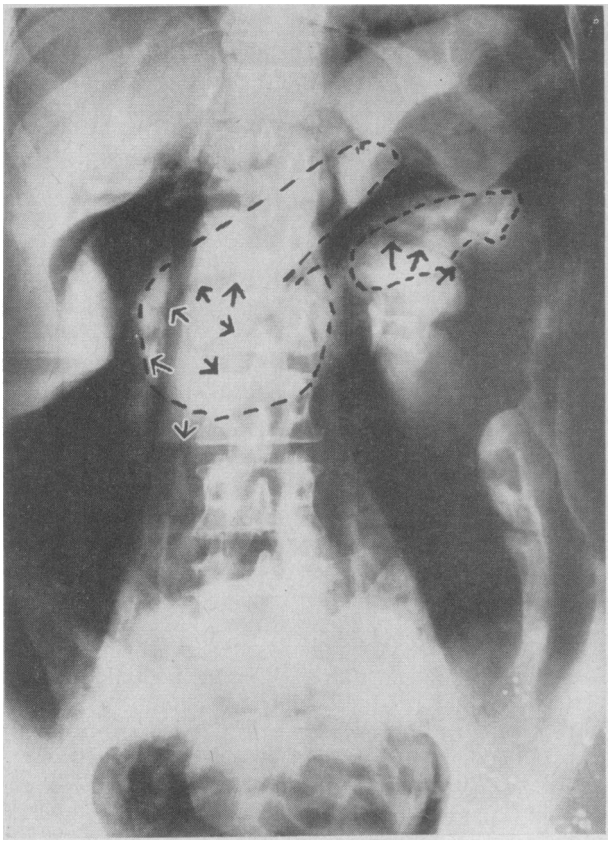

Fig. 1.—Mrs. O.D., Hosp. No. 66841. Intravenous pyelogram and retroperitoneal presacral carbon-dioxide (CO_2) insufflation, March 8, 1961. Fifteen-minute I.V.P. following presacral retroperitoneal CO_2 insufflation showing outline of spleen lying in peculiar transverse position (dotted line), fitting on to and depressing the upper pole of the left kidney (see arrows). The pancreas is also outlined by the dotted line showing the tail displaced upwards and overlying the well-outlined left adrenal. Arrows on the right side of L2-L4 outline a second density which was later recognized as the tumour.

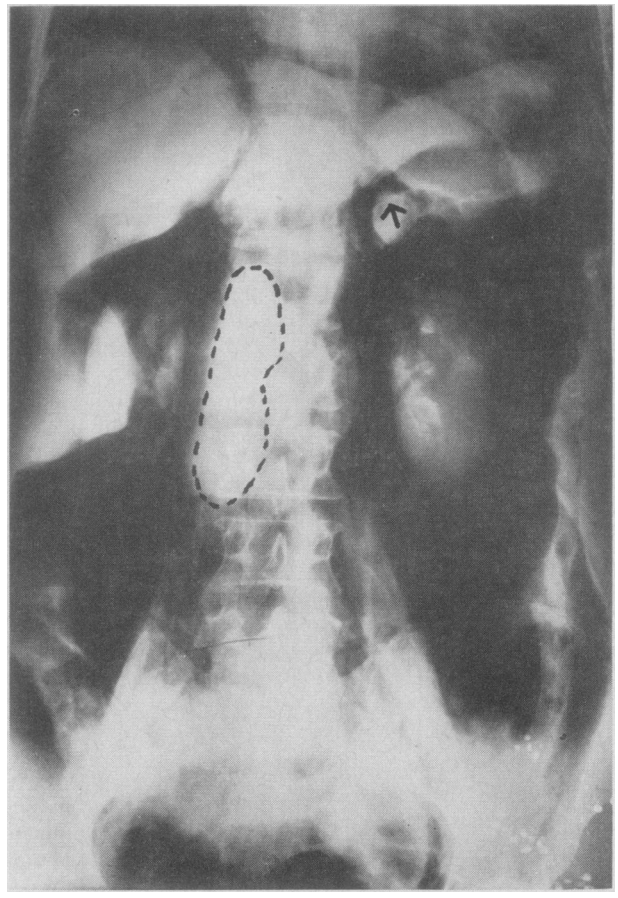

Fig. 2.—Mrs. O.D., Hosp. No. 66841. Intravenous pyelogram and retroperitoneal presacral carbon-dioxide (CO_2) insufflation, March 8, 1961. Denser film of combined retroperitoneal CO_2 and I.V.P. shows persistent outline of "adrenal medulla" within the surrounding adrenal cortex. The dotted outline with more penetration on the film outlines the tumour but not the pancreas or spleen. **Note:** This "adrenal medullary configuration" was consistently reproduced on the majority of films but was, in fact, an adenoma in the tail of the pancreas ectopically and accurately overlying the left adrenal.

DR. E. M. NANSON.* We shall start with the diagnostic problems first. Dr. Spencer, would you please show us the films now?

DR. E. W. SPENCER.† Chest film shows a moderate degree of left ventricular enlargement. The chest is otherwise normal in appearance.

Intravenous pyelograms are normal. However, it is noted that the left kidney is slightly lower than the right.

Intravenous pyelogram and presacral and perirenal air insufflation (Figs. 1 and 2) show nothing abnormal on the right side. The left suprarenal is identified. It measures 3 cm. in diameter and is considered to be somewhat large. Overlying the left suprarenal, and contained within its periphery, there is a rounded area of increased density. This has the appearance of a nodule within the suprarenal. Lying opposite the body of the second lumbar, and projecting to the right of the midline, there is a somewhat lobulated area of increased density, measuring 9 x 4 cm., which has the appearance of a mass of soft tissue. Its nature was not clear. It could represent extension of the tumour, accessory spleen or possibly the pancreas.

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†Professor and Head of Department of Diagnostic Radiology.

DR. NANSON. I am sure Dr. Wolan would like to review the x-ray findings later. Dr. Jaworski, would you care to comment on the problem of clinical diagnosis in this patient?

DR. Z. F. JAWORSKI.* Although we failed to localize the tumour correctly, the diagnosis of pheochromocytoma in this patient was not difficult. Her hypertension was more or less sustained, as is the case in two-thirds of these tumours, but, in addition, she had typical attacks of paroxysmal hypertension. She also manifested excessive sweating, postural hypotension and tachycardia, hypermetabolism without thyrotoxicosis, loss of weight, hyperglycemia during the attacks, and marked nervousness. The presence of several of these manifestations in one patient should arouse one's suspicion as to the possibility of chromaffin tumour.

A few further observations on our patient deserve brief comment. It has been noted previously that a febrile illness in a patient harbouring a chromaffin tumour may induce a severe and continuous rise in blood pressure. In our patient, the

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febrile illness revealed the severity and curious nature of her hypertension. She also showed intermittent albuminuria and a persistently elevated sedimentation rate in the neighbourhood of 90 mm. in the first hour, which promptly fell to normal after the successful operation. Of course, continuous albuminuria is seen in hypertensive cardiovascular disease, and elevation of the sedimentation rate does occur in accelerated and malignant phases of hypertension, but not in uncomplicated essential hypertension. It is uncertain how consistently or specifically intermittent albuminuria and elevation of sedimentation rate occur in cases of pheochromocytoma, although reference to "paroxysmal nephritis" was made in some cases.[18] It is interesting to note in this regard that infusion of catecholamines may result in transient albuminuria.[19] Both these manifestations then are worth remembering.

On physical examination, the discovery of an abdominal mass in a hypertensive patient is of great importance because, if massaging of the mass reproduces a typical attack, the diagnosis is made and the tumour is located for the surgeon. We felt the abdominal mass in our patient but, because no attack occurred on palpation, we considered the mass to be the right kidney in view of its location. The radiological findings suggested that the tumour was located in the area of the left adrenal and thus further diverted our attention from the mass. Probably because of the use of phenoxybenzamine hydrochloride with its blocking action of the catecholamines, the mass and its nature escaped detection when palpated during the first operation.

In the past, many patients would have been explored surgically on the basis of our patient's history and physical findings. If the manifestations of pheochromocytoma are less clear-cut, the diagnosis is further corroborated by either provocative or blocking tests. The results of phentolamine (Rogitine) and histamine tests were unequivocally positive in this patient. However, these tests are indirect and are liable to show both false negative and positive results. The phentolamine test is notorious for giving false positive results in patients who have been given sedatives or tranquillizers, and also in those with renal insufficiency. The histamine test is not without danger, since vascular accidents may occur during the induced hypertensive attack. In our patient, two intravenous injections of 5 mg. phentolamine had to be used at two-minute intervals to bring the resultant severe rise in blood pressure under control.

Recently, Gitlow *et al.*[4] devised a simple colorimetric test for pheochromocytoma based on a semiquantitative estimation in the urine of a final metabolite of catecholamines, 3-methoxy-4-hydroxymandelic acid.[4] Prior to our patient's operation, the result of this test was consistent with the diagnosis of pheochromocytoma (Table I). Twenty-four hours after operation, the test result became negative. If this test continues to give consistent results and, in particular, no false negative results, it may replace the indirect blocking tests and possibly the provocative tests as a screening procedure. The final proof of the existence of chromaffin tumour in a given case must be made, if necessary, by urinary catecholamines estimation.

DR. J. M. CAMPBELL.* This case shows how varied the mode of presentation of these tumours may be and exemplifies various precipitating causes of the acute attack. A rather interesting and curious example of pressure on these tumours is seen when they are present in the bladder wall. There have been ten cases of pheochromocytoma of the bladder reported.[5] In some of these, the acute symptoms are precipitated by voiding. In these circumstances, micturition brings on an attack of weakness, a pounding headache, palpitation and an immediate elevation in blood pressure.

DR. JAWORSKI. Along this line, one should mention that apart from the association of pheochromocytoma with false diabetes, other combinations were noted. There have been 13 cases of pheochromocytoma reported in association with pregnancy, some manifested as pre-eclampsia.[6] Pheochromocytoma is found in a greater proportion of patients with neurofibromatosis than one would expect in the general population. Finally, cases of familial incidence of pheochromocytoma have been reported; in these, the tumour may develop and give rise to symptoms in infants and children.[7]

DR. NANSON. Dr. Woodford, would you please discuss for us the significance of catecholamines in the diagnosis of pheochromocytoma.

DR. V. R. WOODFORD.† The end-products of catecholamine catabolism found in the urine are adrenaline and noradrenaline as such, their sulfate or glucuronide conjugates, their 3-methoxy derivatives and 3-methoxy-4-hydroxymandelic acid, as well as 3,4-dihydroxymandelic acid. The catabolism of the catecholamines has been ably summarized by Axelrod.[8]

Many methods have been devised for the estimation of the catecholamines and their derivatives. Some of these measure both noradrenaline and adrenaline excretion while others measure the excretion of a common end-product of metabolism; for example, the measurement of 3-methoxy-4-hydroxymandelic acid does not distinguish between adrenaline or noradrenaline metabolism. The method in use in our laboratory for the estimation of the urinary excretion of adrenaline and noradrenaline is that of Drujan *et al.*[9] Mean normal values obtained by these authors are about 16 μg./24 hr. for adrenaline and 55 μg./24 hr. for noradrenaline. Normal ranges were: adrenaline 3-31 μg./24 hr., and noradrenaline 25-130 μg./24 hr.

The results of the estimations for urinary catecholamines for Mrs. O.D. are presented in Table

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II. These results show that the excretion of both noradrenaline and adrenaline were higher than normal. The value obtained for noradrenaline on the tenth day before operation is of special interest. On this day, the patient had a hypertensive attack which was accompanied by an increased noradrenaline excretion amounting to more than twice as much as that excreted on any of the previous three days.

Postoperatively the catecholamine excretion was diminished (Table II). A steady fall in the output of both adrenaline and noradrenaline occurred during the second, third and fourth postoperative days to values within the normal range.*

It is interesting to speculate that the steady fall in catecholamine excretion during the three postoperative days investigated represents a slow release of these substances from extra-tumour storage sites.

The adrenaline formed in the body is formed almost entirely in the adrenal medulla, where the adrenaline to noradrenaline ratio is approximately 5:1. Noradrenaline is produced at the effector endings of the adrenergic nerves and, in the fetus, by the organ of Zuckerkandl. In the overall excretion of catecholamines from the body, the proportion of urinary noradrenaline is much greater under normal conditions than that of adrenaline. There is thus a theoretical basis for the suggestion by von Euler[10] that analyses of urinary adrenaline and noradrenaline might reveal whether the pheochromocytoma is of adrenal medullary origin or is of extra-adrenal origin.

Crout and Sjoerdsma[11] have presented evidence to show that if the adrenaline excretion is elevated, the site of the tumour is most likely to be in either the adrenal gland itself or the abdomen close by. If only the noradrenaline excretion is elevated, the site of the tumour may be anywhere in the body. If these relationships hold, then the differential estimation of adrenaline and noradrenaline may be of some assistance to the surgeon in locating the site of the tumour.

Analysis of the tumour after removal from the patient revealed the catecholamine concentrations which are presented in Table III. These values fit into the range reported in the literature.[12]

TABLE III.—CATECHOLAMINE CONTENT OF THE TUMOUR

Mrs. O.D., Hospital No. 66841.

	Adrenaline	*Noradrenaline*	*DOPAmine*	*Total CA*
µg. per mg. (wet weight)	0.14	3.42	0.16	3.72
mg. in tumour (tumour weight =72 g.)	10	246	12	268

*Analyses for adrenaline and noradrenaline carried out on days 48 and 49 postoperatively gave values equivalent to those of the fourth postoperative day, indicating that by this time the catecholamine excretion had returned to its characteristic level.

DR. NANSON. The problem in regard to this patient was that she had had an exploration of her left adrenal area where the pheochromocytoma was thought to be located. This had been carried out by Dr. C. T. Wolan and no obvious tumour had been found in the left adrenal area. At the time of the left adrenal exploration, which was carried out through a left kidney incision, the peritoneum was opened and Dr. Wolan had explored the rest of the abdomen as well as he could through this incision. He did not locate the tumour, however.

After this first exploration, repeated biochemical studies showed that this person must have a pheochromocytoma. There was no indication that this tumour existed above the diaphragm. Chest radiographs were entirely normal. There was no lesion to be found in the neck. Therefore, it was likely that the tumour was in the abdominal cavity. The differential urinary catecholamine determination strongly supported this view. The possible locations where it might be found were in the right adrenal area, in the paraganglionic area related to the sympathetic chain, or in the area of the organs of Zuckerkandl.

It was therefore decided that this patient must have a laparotomy. Accordingly, this was carried out on April 6. After anesthesia had been induced, an indwelling intra-arterial needle was placed in the right femoral artery and connected to a transducer which gave us a continuous blood pressure record both on a recording photographic chart and also on an oscilloscope. At this stage, the patient was purposely not blocked with any ganglionic blocking agent.

The abdomen was opened through a right midparamedian incision and exploration was carried out. Firstly, the left adrenal area was re-explored and no abnormality was found there. The right adrenal area was also explored and no abnormality was found there. Then, on exploring along the right side of the vertebral column, it was evident that there was quite a large tumour situated in front of the inferior vena cava and behind the second and third parts of the duodenum. This was a tumour of about 5 cm. in length by 2-3 cm. in width. It was moderately firm. On palpation of this tumour, an immediate rise in the blood pressure occurred, indicating that we were dealing with a functional pheochromocytoma. The duodenum was therefore carefully reflected off the front of the tumour by incising the peritoneum along its lateral aspect and the dissection of the tumour was carried out. This was done very gently. It was found that two veins were passing from the tumour into the anterior surface of the inferior vena cava. These were clamped and divided. As soon as we began to manipulate the tumour in its dissection, the blood pressure began to rise and therefore the anesthetist, Dr. J. C. Kilduff, controlled this rise with intravenous injections of Rogitine. When we came to the dissection around the draining veins which went into the front of

the inferior vena cava, the blood pressure rose quite considerably to 300 mm. Hg, and further injections of phentolamine (Rogitine) were required. The tumour was removed without difficulty and slowly over the next five to ten minutes the blood pressure fell quite considerably. At this stage, a noradrenaline drip was set up to maintain the pressure at a satisfactory level. The abdomen was closed in a routine manner. Following the operation, the patient had an uninterrupted convalescence.

DR. NANSON. Dr. Braun, what was the tumour like histologically?

DR. E. H. BRAUN.* The specimen consisted of a pinkish-grey, well-encapsulated mass, weighing 74 g. and measuring 10.5 x 4.8 x 27 cm. Histologically, it is a well-differentiated and benign-looking pheochromocytoma. Sections fixed in chromate solution revealed typical minute, brown, cytoplasmic granules.

DR. NANSON. Dr. Kilduff, the choice and conduct of anesthesia were important to the surgeon. Would you care to comment on this?

DR. C. J. KILDUFF.† This patient was presented for anesthesia and surgery first with the diagnosis of pheochromocytoma in the left adrenal area.

After consultation with Professor Mark Nickerson, it was decided to give phenoxybenzamine HCl (Dibenzyline HCl) intravenously to the patient. Dibenzyline HCl is highly effective in the specific blockade of excitatory responses to adrenergic stimuli. It has also been used to prevent cardiac arrhythmias.

The day before the operation this patient was given 1 mg. Dibenzyline/kg. body weight intravenously. Blood pressure before the administration was 210/120 mm. Hg and pulse rate 84 per minute. After 90 minutes, the blood pressure was 80/60 mm. Hg, during which time 25 mg. of Dibenzyline was given. The intravenous infusion was stopped for 15 minutes, whereupon the blood pressure rose to 120/80 mm. Hg after bandaging of the legs and placing the patient flat. The remainder of the drug was given during the next fifteen minutes without any changes in blood pressure, which also remained stable during the night.

The next morning the same dose of Dibenzyline was given 90 minutes before induction of anesthesia, without any further change in blood pressure. Endotracheal anesthesia was maintained with sodium thiopental, nitrous oxide–oxygen and an azeotropic mixture of halothane and ether with d-methyl-tubocurarine added for relaxation. Respirations were controlled during surgery.

Blood pressure dropped momentarily when the periosteum was being stripped from the left twelfth rib and during exploration of the abdomen with the patient in the acutely flexed kidney position.

The tumour was not found during this operation. After three hours of anesthesia, blood pressure had risen to 160/100 mm. Hg and reached 200/120 mm. Hg in 10 minutes, having averaged 120/80 mm. Hg during the operation.

Dibenzyline was not used during the second operation, as there was now some doubt as to the exact location of the tumour. It was decided to control blood pressure with phentolamine and noradrenaline.

General anesthesia was conducted in the same fashion as during the first anesthetic.

Before anesthesia, blood pressure was 220/120 mm. Hg and fell to 125/90 mm. Hg after induction and remained so until the peritoneum was opened. The tumour was located and, on manipulation of the tumour, the blood pressure rose to 270/120 mm. Hg with a bout of cardiac arrhythmias. Manipulation was stopped temporarily and the blood pressure and arrhythmias were controlled with 5 mg. phentolamine intravenously. This dose was repeated on another five occasions to control the blood pressure; cardiac arrhythmias were infrequent after the first occasion.

On removal of the tumour, the blood pressure immediately fell from 270/130 mm. Hg to 110/90 mm. Hg and then to 80/60 mm. Hg over the next 15 minutes. Noradrenaline administration was delayed for five minutes after removal of the tumour to eliminate the possibility of a second tumour. It was then begun as an intravenous drip. Twenty minutes after noradrenaline was started, the blood pressure started to rise and reached 120/80 mm. Hg in 10 minutes, at which time the operation was finished.

The patient remained for 45 minutes on the operating table to stabilize. One hour later she was fully awake in the recovery room.

Blood pressure maintained itself at approximately 120/80 mm. Hg. Noradrenaline was discontinued after four hours and 45 minutes without any change in blood pressure.

The total dose of noradrenaline used was 0.04 mg.

This was a very interesting case as it gave a very rare opportunity to use two different techniques to control blood pressure in the same patient within a short period of time. It also demonstrated that manipulation of the tumour, although not recognized at the time owing to the type of incision in the first operation, did not alter blood pressure or produce cardiac irregularities when the patient was blocked with Dibenzyline. The unblocked patient during the second operation demonstrated the hazards of the phentolamine method.

Cardiac arrhythmias are not uncommon during anesthesia and their incidence is increased by a high level of catecholamines. The hypertensive crises can give rise to acute pulmonary edema or cerebral hemorrhage. Prolonged use of noradrenaline intravenously can lead to local damage of the

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limb and produce a ganglionic type of blockade which makes the patient very dependent upon noradrenaline.

The use of phenoxybenzamine with an exploratory laparotomy would appear to make the anesthesia and surgery safer for the patient. It does make the localization of a very small tumour and secondary tumours more difficult. Small tumours are more likely to produce a lower level of catecholamines than this large tumour and make the use of either technique safer.

DR. NANSON. Dr. Wolan, do you agree with Dr. Kilduff's statement that use of phenoxybenzamine with an exploratory laparotomy does not make the surgeon's task more difficult in finding or identifying the tumour?

DR. C. T. WOLAN.* In hindsight, if we had not been so certain that the left adrenal contained the tumour and attacked it directly as we did, maybe it would not have been advisable to "block" the patient preoperatively because certainly during the four palpations of the "duodenum" she would have become hypertensive and given us a clue. This is particularly true with the femoral catheter and pressure recording hook-up that we used for the second operation.

DR. NANSON. Dr. Wolan, what do you think of retroperitoneal air as a diagnostic tool in localizing pheochromocytoma?

DR. WOLAN. In this particular case it was misleading and we did not interpret the findings properly. Since the majority of these tumours occur in the adrenal, if the adrenal can be adequately visualized with retroperitoneal air insufflation it certainly is a good clue to the diagnosis. Presacral retroperitoneal carbon dioxide insufflation is a relatively safe and good procedure.

DR. NANSON. Would you care to say a few words about this particular case, Dr. Wolan?

DR. WOLAN. Hindsight is a wonderful thing. It has taught us several lessons. When I palpated intra-abdominally through a rent in the peritoneum from the left flank, I could not feel any masses or nodules along the course of the right sympathetic chain. The whole left sympathetic was previously visualized retroperitoneally. Nothing palpable was felt in the region of the right adrenal, with the kidney feeling normal as well. We identified what we thought to be the second part of the duodenum, retroperitoneally, on four separate palpations and thought out loud, "This is the duodenum. This is the right kidney and it feels normal. Here should be the adrenal and it cannot be felt. There certainly is no fullness or nodularity here." We also felt the preaortic and the subaortic areas within the pelvis. The whole right sympathetic chain area was also palpated and nothing was found.

May we have the second films shown, Dr. Spencer?

There is a little too much CO_2 in these films (Figs. 1 and 2) because, for some reason, it did not absorb as quickly as it often does. See this rounded mass here, lateral to the body of the third lumbar vertebra? In our conference prior to the second operation, I said that this rounded figure bothered me and asked Dr. Nanson if it was the duodenum end where the second part meets the third. Dr. Nanson replied that he had never seen the duodenum with retroperitoneal air studies and could not say. After having viewed the tumour behind the second portion of the duodenum, between it and the vena cava, we can see that it exactly fits the location and outline of the tumour. Here is what we so definitely thought was the tumour in the medulla of the adrenal. It is consistent on all the films. This, in retrospect, is the adenoma in the tail of the pancreas which we biopsied. It is fixed in this area, with the tail of the pancreas being much more superior than is usual. Here is the rest of the pancreas and here is the tumour. The adenoma of the tail of the pancreas superimposed on the adrenal so regularly and persistently was a "red herring".

We also wondered about this rounded mass below the bifurcation of the aorta in front of the upper portion of the sacrum. This undoubtedly is sigmoid on end, but that is why we asked Dr. A. B. Brown to see her and do a pelvic examination to see if he could feel something above the uterus. The pelvic examination was reported as negative. We have all, and I in particular, learned a good lesson from this case.

DR. NANSON. I think there are one or two important points to be made in connection with the surgery of a patient suspected of having a pheochromocytoma. I feel rather strongly that the difficulty of accurate localization of the tumour is such that these patients should always be explored by means of a laparotomy. It is very important to be able to explore all the possible areas where a pheochromocytoma might exist, namely, both adrenal areas where some 90% of the tumours will be found, together with the para-aortic areas along the sympathetic chains and the area of the organs of Zuckerkandl below the bifurcation of the aorta. The second point of importance is, I think, the virtue of monitoring the blood pressure continually by means of an indwelling intra-arterial needle. If there is any doubt about a tumour, the palpation of the suspected area may demonstrate a sharp rise of blood pressure, which is highly significant in so far as it indicates that the area that is being palpated is the seat of a tumour which is producing a vasopressor. I think it is unwise to block these patients in advance before the exploration has been carried out, as you may prevent elicitation of this useful sign of a rise of blood pressure associated with palpation of the tumour. The third point is that, having removed the tumour, it is important to explore the other areas where tumours may be found, as occasionally these

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tumours are multiple. Fourthly, during the removal of the tumour, manipulation should be as gentle as possible, and if there is a rise of pressure at this time, the anesthetist should block the effect of the catecholamines so released by means of Rogitine. This worked very well in this tumour and at no time gave us undue concern. The fifth point is that when the tumour is removed there may be a fall of pressure to a degree that a vasopressor is required and noradrenaline is the ideal drug for this and a noradrenaline drip should be maintained to produce an adequate blood pressure until such time as it is no longer required.

It is important in exploring the abdomen to make sure that there are two normal adrenal glands. Occasionally one may be absent or atrophic and, if the tumour is located in the good adrenal gland, then the removal of this may precipitate the patient into an adrenal deficiency state.

One of the striking features in the postoperative state of this particular patient was the feeling of well-being that resulted once the tumour was removed, with the decrease in the symptoms of nervous tension which she had before the operation.

Dr. Hoffer, you saw this lady. Have you any comments on the emotional reactions to catecholamine excess?

DR. A. HOFFER.* The relationship of adrenaline to mood is a very interesting one. Surgeons are especially interested in the connection between adrenaline and pheochromocytoma. Internists are interested in its relationship to blood pressure. Psychiatrists are interested in the possible connection between mood and adrenaline.

We in psychiatry have tended to look upon depression as primary, that is, as a cause which would elevate adrenaline levels. This case, however, illustrates that the increased secretion of adrenaline can be a cause of irritability and depression. There are many cases in the literature where this has indeed been the case and many of us in the field of psychiatry are now becoming concerned about determining which really is cause and which is effect.

This patient was clearly tense, irritable and depressed. I gave her an HOD test.[13] I have given this test to a large series of patients. From the test it is possible to arrive at a depression score. The mean score for a hundred normals was 0.87 with only four normals scoring 4 or more and the highest score being 5. The mean of one hundred patients examined in a random series was 7.76. Only ten scored between 0 and 3, and 90 scored over 4. This difference, of course, is highly significant. This patient was given the test and it was asked that she complete it on the basis of her feeling for the month before her operation. She had a depressive score of 7. It was, of course, quite obvious from her history even without this simple test that she had been quite irritable and depressed. A couple of days later, after the operation, she was asked to do the test on the basis of her feeling since the operation and this time her depression score was zero.

It is therefore likely that this patient was depressed owing to her excessive secretion of adrenaline and also because of her feeling that perhaps the physicians would not be able to find the cause of her problem and therefore would be unable to treat it.

I was especially interested in the very high levels of sympathomimetic amines found in the urine. It is well known that only about 1% to 4% of these compounds when given by vein appear free in the urine, so that one can logically give a correction factor of perhaps 50-100. If one does this, it is quite obvious that she was secreting many milligrams per day. The question is—how was she able to tolerate so much? With animals, one can give increasing quantities of adrenaline to which the animal adapts and perhaps this is what happened in this case.

Dr. Manger used serum levels of adrenaline-like substances.[14] At the Mayo Research Foundation they suggest that 6.8 μg. per litre indicates pheochromocytoma. With essential hypertension, the range is 1.5-1.8, whereas with normal people it is much less.

This case, therefore, is another example of the inter-relationship of certain chemical hormones to mood.

DR. NANSON. Dr. Jaworski, how successful have we been in curing this lady?

DR. JAWORSKI. There are two aspects to be considered in the prognosis for a case of pheochromocytoma. Firstly, occasionally there is the problem of recurrence of tumour and hypertension after a variable period of time following successful surgery. The question then arises as to whether one is dealing with the development of a new tumour or the metastasis from the original tumour. Only 10% of pheochromocytomas are malignant, but both histologically and clinically it may be difficult to decide whether one is malignant or benign. Both types may infiltrate locally and grow in blood vessels. The fact that a tumour is well encapsulated does not guarantee that it will not metastasize. A case reported in Canadian literature by Belkin, McQueen and Duffin[15, 16] bears out this fact. On the other hand, there are reports of recurrences of hypertension due to the development of another chromaffin tumour *de novo*.[17] On a statistical basis, the chances are good that our patient's pheochromocytoma was benign and will not recur.

Secondly, the prognosis in these cases will depend on the effect of the removal of the pheochromocytoma on the blood pressure. In many instances removal of the tumour or, for that matter, removal of any specific cause of hypertension, may not result in return of the blood pressure to normal.

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The left ventricle, the arteries and the arterioles, and hence the perfusion and the health of the myocardium, the cerebral and renal parenchyma, all may have been compromised by the hypertension due to a specific cause and these changes, including hypertension, may become irreversible. Some think that irreversible hypertension in these instances is due to secondary renal involvement. In our patient, renal function was grossly normal but there were definite hypertensive retinal changes, and left ventricular hypertrophy, and her blood pressure following operation did not return to normal although it was greatly diminished. It is suggested that false negative Rogitine tests in some cases of pheochromocytoma may be due to the fact that irreversible hypertension is already established. Considering that hypertension of any cause may become irreversible, one should attack the remedial and specific causes without undue delay. We do not know at the present time what course the hypertensive cardiovascular disease will take in our patient.

DR. NANSON. Thank you, gentlemen, for your attention. Our time is up, but I think you will agree that this patient with pheochromocytoma has served a most useful purpose. She has been the means of synthesizing the departments of medicine, surgery, anesthesia, biochemistry, pathology, psychiatry and radiology over a common problem. In our turn, I hope we have helped her.

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REVIEW ARTICLE

RECTAL BLEEDING IN INFANCY AND CHILDHOOD*

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FEW SYMPTOMS cause a mother to seek medical attention for her child with greater dispatch than does that of the appearance of fresh or altered blood associated with the stool. This is indeed fortunate for, while the cause may be inconsequential, this symptom may herald the presence of serious disease requiring urgent therapy and even emergency surgery.

The recent occurrence of three instances of severe bleeding from the rectum in children in my practice has prompted me to examine the records of such cases in this area and survey the rather meager literature on the subject. It soon became apparent that the standard coding of discharge diagnoses of hospitalized patients did not make it possible for record librarians to provide charts of patients on a basis of their presenting complaint with any consistency. In response to a request for the records of all patients under the age of 16 with rectal bleeding or melena in two Edmonton hospitals only 63 charts were made available. None of the personal cases were included in the records provided because they were discharged as Meckel's diverticulum, thrombocytopenic purpura and gastrointestinal angiomatosis. A complete review of local experience was therefore virtually impossible. The excellent classification of Koop[7] has consequently been selected as the background against which selected cases will be discussed in an attempt to clarify the differential diagnosis and treatment of rectal bleeding in infancy and childhood.

*Presented at the Annual Meeting of the Saskatchewan Division of the Canadian Medical Association, October 18-21, 1960, and the Annual Meeting of the Alberta Division of the Canadian Medical Association, September 25-28, 1961.
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SYMPTOMATOLOGY

There is rather universal agreement that a carefully elicited history is frequently the most valuable part of the evaluation of any case of rectal bleeding. The following points must be established, if at all possible.

1. *How Much Blood Has Been Passed?*

This information may help with the diagnosis but is even more important in the assessment of the urgency of the situation. It must constantly be kept in mind that the loss of a quantity of blood which in the adult would be inconsequential may